

A Multimodal Study of Brain Glutamate Levels, Hyperactivation, and Neurodegeneration in Prodromal Alzheimer's Disease

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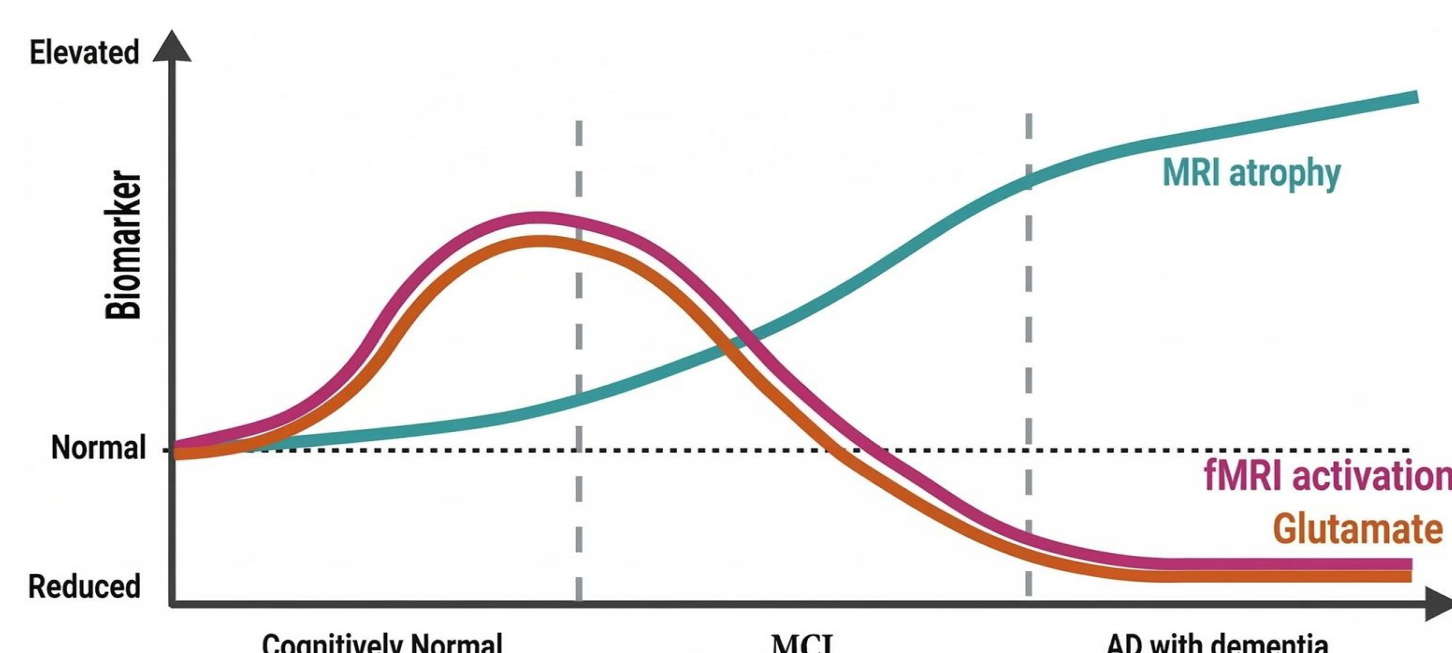
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Glutamate levels 1) are positively associated with functional activation, 2) show an inverse U-shaped relationship with neurodegeneration, and 3) mediate the relationship between neurodegeneration and functional activation, suggesting a mechanistic role.

BACKGROUND

- Functional activation follows an inverse U-shaped trajectory as neurodegeneration progresses. (Corriveau-Lecavalier et al., 2020)
- Glutamate (Glu) has been proposed as a key driver of this hyperactivation. (Zott et al., 2019)
- While demonstrated in animals, evidence in human prodromal Alzheimer's disease (AD) remains limited.

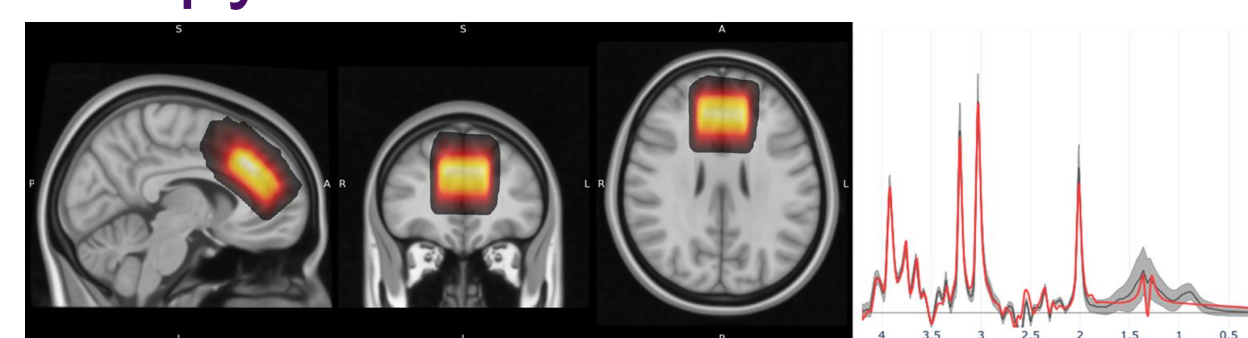
Hypothesized glutamate trajectory in relation to functional activation and structural atrophy



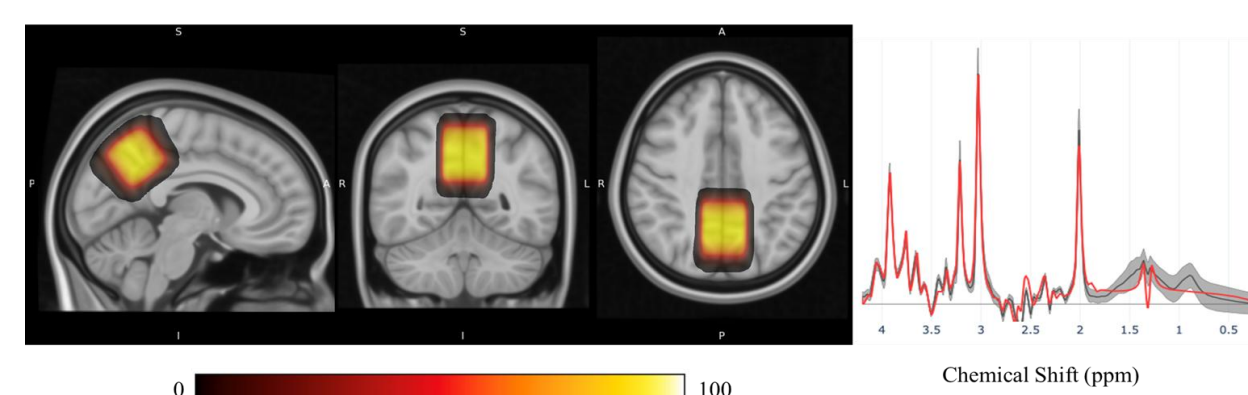
METHODS

- N = 107 individuals from the CIMA-Q cohort, including cognitively unimpaired, subjective cognitive decline+, and mild cognitive impairment. (Belleville et al., 2019)
- Glutamate levels measured with magnetic resonance spectroscopy.

Anterior Cingulate Cortex (ACC)



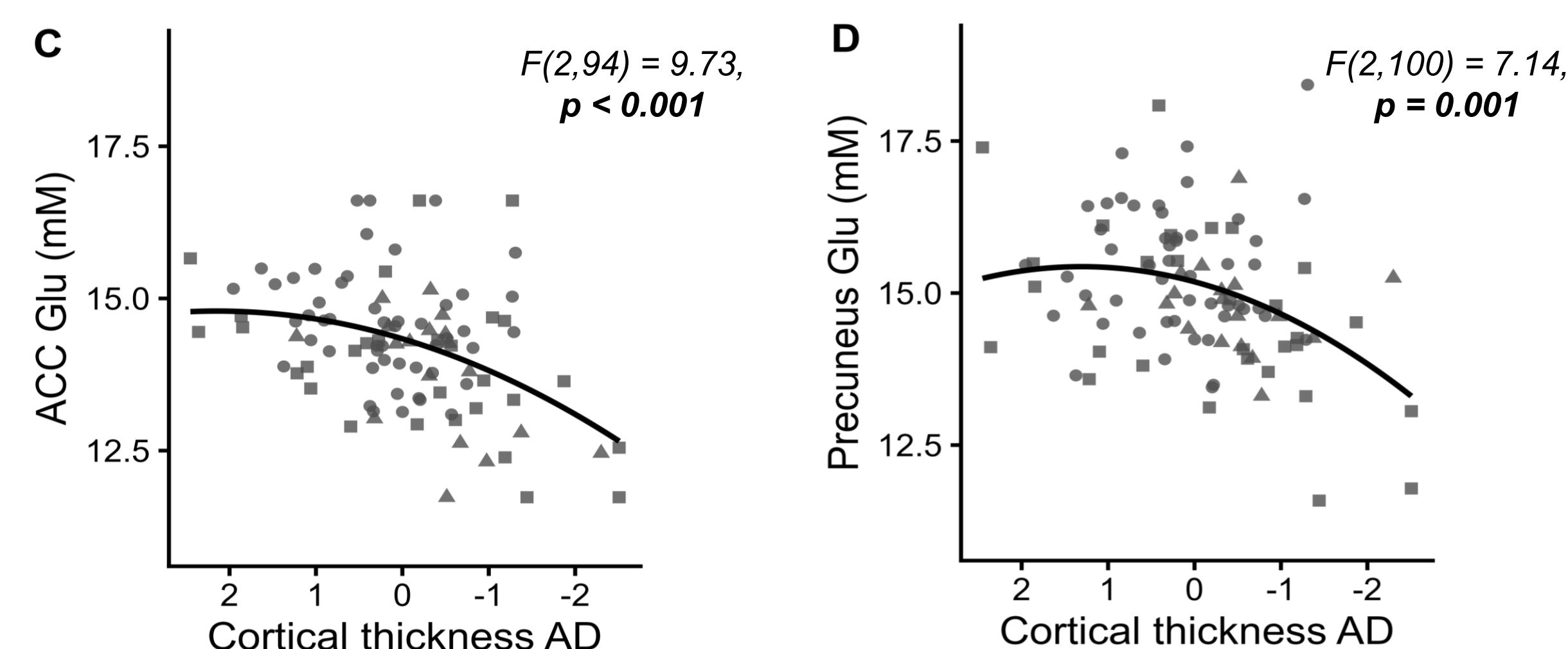
Precuneus



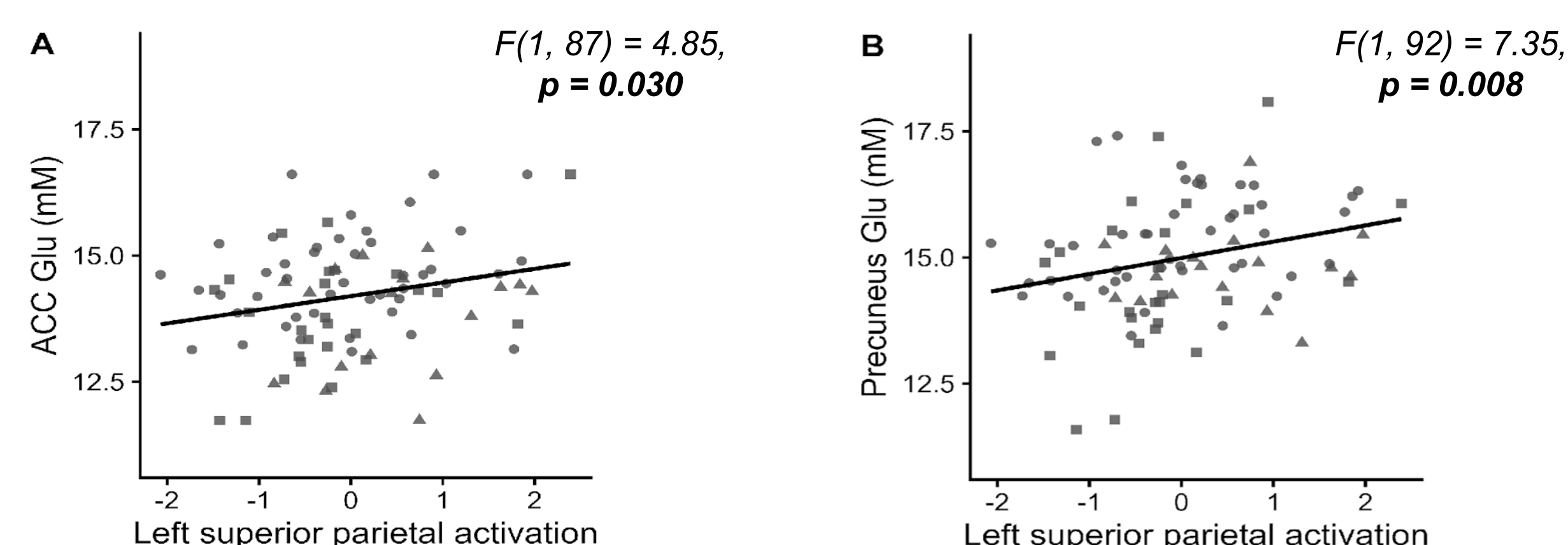
- Activation was measured using task-based functional magnetic resonance imaging during an associative memory encoding task, focusing on the left superior parietal lobe and hippocampus.

RESULTS

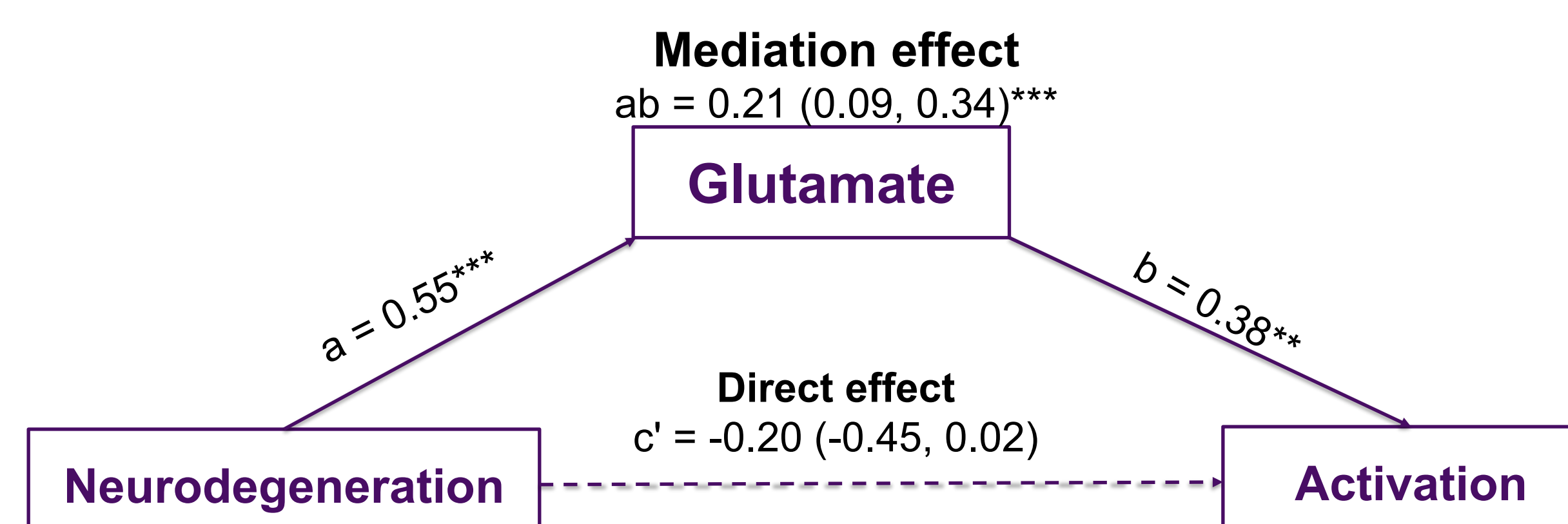
Inverse U-shaped relationship between markers of neurodegeneration and glutamate



Positive linear relationship between activation and glutamate



Glutamate mediates the relationship between neurodegeneration and activation



Statistical Analysis: Polynomial modeling and causal mediation analysis.

CONCLUSIONS

- Glutamate is positively associated with functional activation.
- Glutamate follows an inverse U-shaped relationship with neurodegeneration, mirroring the relationship between neurodegeneration and hyperactivation.
- Glutamate mediates the relationship between structural neurodegeneration and functional hyperactivation.
- Mechanism:** These findings support glutamate as a key factor underlying hyperactivation.
- Impact:** glutamate emerges as an early pathophysiological contributor in AD, involved in the transition between hyper- and hypoactivation in early disease stages.

REFERENCES & CONTACTS

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References



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